A Phase I Study of Intralesional Administration of an Adenovirus Vector Expressing the HSV-1 Thymidine Kinase Gene (AdV.RSV-TK) in Combination with Escalating Doses of Ganciclovir in Patients with Cutaneous Metastatic Malignant Melanoma.

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(2) NON-TECHNICAL ABSTRACT

This clinical trial will test the effect of higher doses of the antiviral drug ganciclovir (GCV) combined with *herpes simplex* virus-1 thymidine kinase (HSV-tk) gene transfer in patients with advanced malignant melanoma. Malignant melanoma is an aggressive form of skin cancer often caused by excessive sun exposure. Once metastasized (spread), surgery cannot cure melanoma. Malignant melanoma often does not respond to radiation, chemotherapy or immune stimulating drugs and the prognosis for patients with advanced disease is poor. Gene therapy, the genetic modification of human tissues and cells for therapeutic benefit may offer a new approach to treatment of melanoma and other refractory cancers. Several cancer gene therapy trials have used the transfer of viral or bacterial genes into tumor cells to sensitize them to ordinarily non-toxic drugs, so called "suicide" gene therapy. The best studied of these systems is HSV-tk combined with GCV. HSV-tk is an enzyme found in *herpes simplex* virus ("cold sore" virus) that is important in allowing virus to make new DNA to replicate itself. GCV can be used to treat *herpes* infections because HSV-tk converts GCV to a toxic form that kills the virus and the cell that it has infected. Normal cells lacking HSV-tk remain unaffected because they have difficulty converting GCV to its active form. Adenoviruses, a different type of common "cold" virus have been genetically engineered to carry the HSV-tk gene because these viruses can easily infect and transfer the HSV-tk gene to human cancer cells. More than 20 clinical trials are now open involving the use of the HSV-tk/GCV suicide gene therapy for treatment of various cancers. An early review of the results of these trials have found a tumor response rate of about 13%. To date the results of two of these trials have been published in their entirety: Researchers at the NIH implanted mouse cells into the brain tumors of patients that produced another type of virus (retrovirus) expressing HSV-tk in an attempt to infect the surrounding brain tumor cells with the HSV-tk gene. The patients subsequently received a standard intravenous dose of GCV 5 mg/kg twice daily for 14 days. Successful gene transfer was shown in two biopsied lesions and 5/19 treated lesions responded to therapy. The duration of response, however, was short. In another trial conducted at the University of Pennsylvania, 21 patients with malignant mesothelioma (a cancer of the lining of the lungs) were treated with increasing doses of an HSV-*tk* expressing adenovirus followed GCV 5 mg/kg I.V. twice daily for 14 days. Successful gene transfer was shown in 11 of 20 patients, however, no tumor shrinkage was seen despite high doses of the virus administered to patients.

Research performed in the Clinical Gene Therapy Branch, NHGRI has indicated an improved ability to kill HSV-tk expressing tumor cells as the dose of GCV is increased (a dose-response effect). Furthermore, studies have shown that the blood levels of GCV achieved in mice with the doses used in preclinical experiments are substantially higher than that seen in patients with standard clinical dosing (5 mg/kg twice daily). GCV was developed and approved as an antiviral drug to treat immunosuppressed bone marrow transplant, leukemia and AIDS patients with serious *herpes* virus infections and not for HSV-tk/GCV cancer gene therapy. This has lead to dosing recommendations in these diseases that may not be appropriate in the setting of HSV-tk cancer gene therapy. We propose that the low response rate reported to date in HSV-*tk*/GCV cancer gene therapy trials may in part be a result of inadequate dosing of the prodrug ganciclovir. This study will attempt to address the clinical ganciclovir dose-response effect in an adenovirus mediated HSV-*tk* gene therapy trial in patients with advanced melanoma.

Adult patients with advanced (stage IV) malignant melanoma who are not curable by currently available treatments and who have at least one accessible melanoma tumor on or just under the skin will receive injections of a genetically engineered adenovirus expressing the HSV-*tk* into the tumor at a fixed dose. Forty-eight (48) hours after injection of the virus, patients will receive intravenous GCV every twelve (12) hours for seven (7) days. This study will involve the escalation of the total dose of GCV administered to groups of patients. Each group will receive increased dosages with 2.5 mg/kg increments from an initial 5 mg/kg to a maximum 20 mg/kg every 12 hours until unacceptable side effects are seen. Each patient group (cohort) will receive only one dose level of GCV. Patients will be closely monitored for toxic side effects of the treatment. Patients will also be evaluated for response of their melanoma to treatment (both the treated lesion and other sites of untreated disease). Patients will undergo blood sampling to determine the blood levels of GCV and the effects of this treatment on various blood immune hormone (cytokine) levels at different time points during the treatment. The goal of this study is to determine the maximum tolerated dose (MTD) of GCV which can be administered in combination with adenoviral mediated HSV-tk (AdV.RSV-TK) gene transfer, and the dose-limiting toxicity (DLT) of HSV-*tk* gene therapy in combination with high dose GCV in skin tumor patients before proceeding to other clinical trials where tumor may involve deep internal organs. A secondary goal will be to determine the response of the treated, remote untreated lesions and the blood levels of GCV achieved at these doses.